REMARKS

Claims 122, 185, 189, 192, 197, 200, 221-224, 226, 228-232 are pending and under active consideration.

Claims 122 and 178 have been amended for clarity. The support for the amendment to recite "wherein at least two of the probes are complementary and hybridizable to genomic sequences contained entirely within an intron" can be found in the specification as originally filed, *inter alia*, on page 15, lines 23-27 and page 30, lines 14-15.

It is believed that no new matter has been added by the amendments made herein. Entry of the foregoing amendments is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The rejection of claims 122, 185[1], 189, 192, 197, 200, 221-222, 224, 226 and 228-232 under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,329,140 by Lockhart ("Lockhart") in view of Bowtell, 1999, Nature Genetics Supplement 21:25-32 ("Bowtell") is maintained for the reasons of record. Also maintained is the rejection of claim 223 as obvious over Lockhart and Bowtell and further in view of Schena *et al.*, 1996, Proc. Natl. Acad. Sci. U.S.A. 93:10614-19 ("Schena"), for reasons also of record. Applicants respectfully disagree, for the reasons discussed below.

The presently claimed invention relates to positionally-addressable ordered arrays of polynucleotide probes bound to a solid support; wherein the polynucleotide probes comprise at least 100 polynucleotide probes of different nucleotide sequences, each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, wherein the respective genomic sequences complementary and hybridizable to the probes are found at sequential sites in the genome. Further, the amended claims recite that at least two of the probes are complementary and hybridizable to genomic sequences contained entirely within an intron

[1] The Examiner omitted this claim from the statement of the rejection under 35 U.S.C. §103 on page 2 of the Office Action, apparently inadvertently.

(which intron can be the same intron or different introns for the respective at least two probes).

The claimed arrays are characterized by having (1) a *high density* of the genomic sequences complementary to probes in the genome (because the distance between 5′ ends of the sequential sites is always less than 500 bp), (2) a *large span* of the genomic sequences (because the genomic sequences complementary and hybridizable to the probes span a genomic region of at least 25,000 bp), and (3) at least two probes complementary and hybridizable to genomic sequences contained entirely within an *intron*.

According to the Examiner, Bowtell teaches probes which span a genomic region of at least 25,000 bp, while Lockhart teaches the less than 500 bp distance between 5' ends of sequential probes (Office Action at page 3). However, neither Bowtell nor Lockhart teach or suggest an array where at least two of the probes are complementary and hybridizable to genomic sequences contained entirely within an intron. Thus, the cited references fail to teach or suggest an essential element of Applicants' claimed invention.

Moreover, it would not have been obvious in view of Lockhart and Bowtell to create arrays possessing high density and large span, where at least two of the probes are complementary and hybridizable to genomic sequences contained entirely within an intron. Firstly, Lockhart uses tiling arrays to determine whether a given gene possesses a sequence signature of up to 300 nucleotides or generally up to 300 amino acids (see Lockhart at Abstract, column 1, lines 50-59 and column 7, line 35 to column 8, line 12). While the nucleotide sequence signature can be non-coding (*e.g.*, the TATA box) (see Lockhart at column 7, line 45), there is no disclosure or suggestion in Lockhart of probes hybridizing to intron sequences. Further, the polypeptide sequence signatures taught in Lockhart are clearly expressed as amino acids, and thus would not be probed for intron sequences since intron sequences are not translated into proteins. Regarding the Examiner's assertion that the feature of tiling across non-coding sequences that do not have a sequence signature of interest is not recited in the Applicants' claims (see Office Action at page 4, first paragraph), Applicants point out that the pending claims specify arrays that probe genomic sequences, such that the 5′ ends of the genomic sequences are less than 500 bp apart, and span a genomic region of at least 25,000 bp, and wherein the genomic sequences complementary to at least two of the probes are contained entirely within introns. Because Lockhart teaches that a nucleotide sequence signature of interest does not exceed 300 nucleotides in length and

Applicants' claims specify spanning a genomic region of at least 25,000 bp, Applicants' claimed array would be expected to probe non-coding sequences that do not have a sequence signature of interest. Furthermore, Applicants' claims now recite that at least two of the probes are complementary and hybridizable to genomic sequences contained entirely within introns. Lockhart, however, does not provide any common sense reason to probe genomic sequences that do not have a sequence signature of interest, span at least 25,000 bp, and that are contained entirely within introns.

Secondly, Bowtell deals solely with expression analysis, *i.e.*, the author is interested in analyzing expression of genes, based on using, *e.g.*, ORFs, cDNA, or EST sequences as probes (see Bowtell at page 29, Table 3, columns 1 and 2). Bowtell is not concerned with genomic sequences that are not expressed into proteins, such as introns. Bowtell does not teach or suggest to use probes that are complementary and hybridizable to non-coding intron sequences, much less probes that are complementary and hybridizable to genomic sequences contained entirely within an intron. In fact, such would run counter to common sense based on Bowtell because the use of probes that are complementary and hybridizable to intron sequences would not yield information about relevant protein expression. In one instance, cited by the Examiner on page 6 of the Office Action dated August 17, 2007, Bowtell refers to microarrays containing probes to *S. cerevisiae* genes and particularly to the publication by DeRisi (DeRisi *et al.*, 1997, Science 278:680-686, Reference C97 of record), which describes the generation of microarrays containing probes to *S. cerevisiae* genes obtained by PCR amplification of yeast open reading frames ("ORFs") using genomic DNA (see Bowtell at page 29, col. 2 and Table 3, col. 1; DeRisi at page 680, col. 2 and page 685, note 8). Even though some small percentage of ORFs disclosed in DeRisi may contain intron sequences (because 4% of protein-encoding genes in *S. cerevisiae* contain introns as discussed in Goffeau *et al.*, 1996, Science 274:546-567, Reference C98 of record), the microarray probes taught in DeRisi span entire ORFs and thus cannot be complementary or hybridizable to genomic sequences contained entirely within an intron (see De Risi at page 680, col. 2 and page 685, note 8, and at cmgm.stanford.edu/pbrown (the webpage referred to in DeRisi at page 685, note 9)). Tellingly, neither Bowtell nor DeRisi teach or suggest using probes to genomic sequences contained entirely within an intron. As discussed above, Lockhart does not remedy this deficiency of Bowtell. Further, it would not be obvious for a person of ordinary skill in the art to combine the teachings of Bowtell with the teachings of Lockhart and achieve the claimed invention, because Bowtell does not provide any common sense

reason to probe genomic sequences such that the 5′ ends of the complementary genomic sequences would be less than 500 bp apart, much less where at least two probes are hybridizable to sequences contained entirely within an intron, as called for by Applicants' claims. In fact, such would run counter to common sense, since Bowtell is concerned solely with expression analysis, and, as the Applicants explained in detail in response submitted on October 31, 2007, an array that is capable of monitoring gene expression of even a compact genome of *S. cerevisiae*, though possessing the *large span* called for by the claims, would not possess the *high density* of the claims (Applicants' Remarks in the response filed on October 31, 2007, pages 10-11). Thus, there is no discernible reason, and thus no motivation, in the combination of Lockhart and Bowtell to create an array with a probe set having the *long span*, *high density*, and at least two probes that are hybridizable to genomic sequences contained entirely within an *intron*, as specified in the instant claims.

In response to the Applicants' previously stated argument that there is no specific teaching, suggestion, or motivation to combine Lockhart and Bowtell, the Examiner contends that "the argument that a specific teaching, suggestion, or motivation is required to support an obviousness rejection over prior art is foreclosed by *KSR* (see the recent Board decision *Ex parte Smith*,--USPQ2d--, slip op. at 20, Bd. Pat. App. & Interf. June 25, 2007 which cites KSR...)" (Office Action at page 5). However, in *KSR* the Supreme Court affirmed that it is important "to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007). The Court went further to clarify that "this is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* Furthermore, a recent post-*KSR* Federal Circuit decision explained that a non-rigid "flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis" and merely assures that the obviousness test proceeds on the basis of evidence that arise before the time of invention as the statute requires. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (citing *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). In addition, in *Ex parte Smith* decision cited by the Examiner, the Board of Appeals reiterated the principle affirmed in the *KSR* that it is necessary to determine "an apparent reason to combine the known elements in the fashion claimed by the patent at issue" and that "a court must ask whether the improvement is more than the predictable use of prior art

elements according to their established function." *Ex parte Smith*, Appeal 2007-1925, at 14, Bd. Pat. App. & Interf. June 25, 2007 (emphasis added), available at http://www.uspto.gov.web/offices/dcom/bpai/prec/fd071925.pdf.

Indeed, the arrays of the claims are "more than the predictable use of prior art elements according to their established functions." *See KSR*, 127 S.Ct. at 1740 (citing *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969) and *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976)). The claimed arrays feature at least one element not present in either Lockhart or Bowtell, affording at least one utility not contemplated by either of the cited references. Specifically, this element is the feature of having at least two probes complementary and hybridizable to sequences contained entirely within an intron. The presently claimed arrays, by virtue of their *large span*, *high density*, and the presence of at least two probes that are hybridizable to genomic sequences contained entirely within an *intron*, give rise to a function that is not afforded by the elements of Bowtell and Lockhart relied on by the Examiner. In particular, the claimed arrays can be employed to determine the structure of genes and to precisely identify the boundaries of expressed genes in genomic sequences, for example by delineating intron/exon boundaries, without extensive DNA sequencing of ESTs (see specification at page 3, lines 13-28 and page 4, lines 1-21). This is more than the predictable use of the elements of Lockhart and Bowtell according to their established functions. In contrast, Lockhart uses tiling arrays for signature sequence identification, thereby identifying gene family members having a particular sequence signature. Moreover, the utility of the claimed arrays is not predictable from Lockhart, which in its example teaches probing of coding regions and to avoid probing regions that are near expected intron/exon boundaries:

> The interrogated regions were chosen based on a few criteria: they include regions that are (a) reasonably well conserved (highly conserved at the amino acid level, but less so at the DNA level) and that serve as identifiers of the protein family, (b) highly variable and serve as unique identifiers of individual members of the family, and (c) not near expected intron/exon boundaries.

(see Lockhart at col. 27, lines 11-17, emphasis added). Bowtell uses arrays to determine whether genes are expressed, and thus has no interest in using probes hybridizable to

sequences contained entirely within an intron. Thus, the claimed invention does not employ known elements according to their established functions.

Therefore, claims 122, 185, 189, 192, 197, 200, 221-222, 224, 226 and 228-232 are not made obvious by Lockhart and Bowtell, and the rejection of these claims should be withdrawn.

Finally, with respect to claim 223, the Examiner is using Schena for its disclosure of arrays of probes that measure gene expression using expressed plant genes as controls to support the alleged obviousness of the added limitation of claim 223 (Office Action at page 6). Specifically, the Examiner asserts that it would have been obvious to one skilled in the art to substitute probes taught by Lockhart and Bowtell for expressed genes of plants as taught by Schena because all three references teach arrays for gene expression (Office Action at page 6).

Applicants point out that Schena suffers from the same deficiencies as Bowtell, since Schena is concerned with the use of microarrays containing 1046 random human cDNA clones from a library of Epstein-Barr virus-transformed human peripheral blood lymphocytes, with 10 *Arabidopsis* clones as controls, for monitoring gene expression into proteins (see Schena at page 10614, under "Materials and Methods"). Thus, like Bowtell, Schena is directed at the analysis of gene expression, in this case using cDNAs as probes, with the goal of monitoring expression of the entire human genome. By definition, cDNAs do not contain intron sequences. Schena does not teach or suggest using probes with sequences hybridizable and complementary to genomic sequences contained entirely within an intron. In fact, such would run counter to common sense because use of probes that are complementary and hybridizable to sequences contained entirely within introns would not yield information about gene expression into proteins. Further, one of skill in the art at the effective filing date of the present application would have expected human genes to be separated by 30 kb on average and, accordingly, cDNAs corresponding to adjacent genes to have 5′ sequences complementary to sequences that are, on average, at least 30 kb apart. In contrast, the claims of the present invention call for a distance between 5′ ends of sequential sites of less than 500 bp. Schena provides no common sense reason or any motivation to probe genomic sequences such that the 5' ends of the complementary genomic sequences would be less than 500 bp apart since it is concerned only with protein expression analysis. Accordingly, there is no common sense reason to combine teachings of Schena with

teachings of Lockhart to create an array with a probe set having the *high density* and at least two probes complementary and hybridizable to genomic sequences contained entirely within an *intron*, as specified in the instant claims. *See KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007). Accordingly, Schena does not remedy the deficiencies of Lockhart and Bowtell.

Conclusion Regarding Obviousness

In view of the foregoing remarks, it is submitted that the obviousness rejections are in error and should be withdrawn.

CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

Claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 were withdrawn from consideration by the Examiner as belonging to non-elected species. Since Applicants believe that the generic claims are allowable, claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

Respectfully submitted,

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Enclosures